Tetrahedron Letters,Vol.29,No.20,pp 2437-2440,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

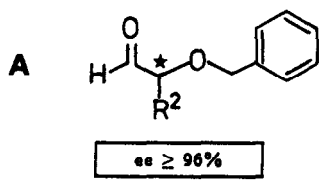
ENANTIOSELECTIVE SYNTHESIS OF PROTECTED α-HYDROXY ALDEHYDES AND KETONES VIA HYDROXYLATION OF METALATED CHIRAL HYDRAZONES

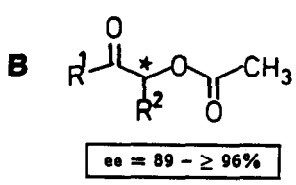
DIETER ENDERS* and VIDYA BHUSHAN

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule
Professor-Pirlet-Str. 1, D-5100 Aachen, FRG

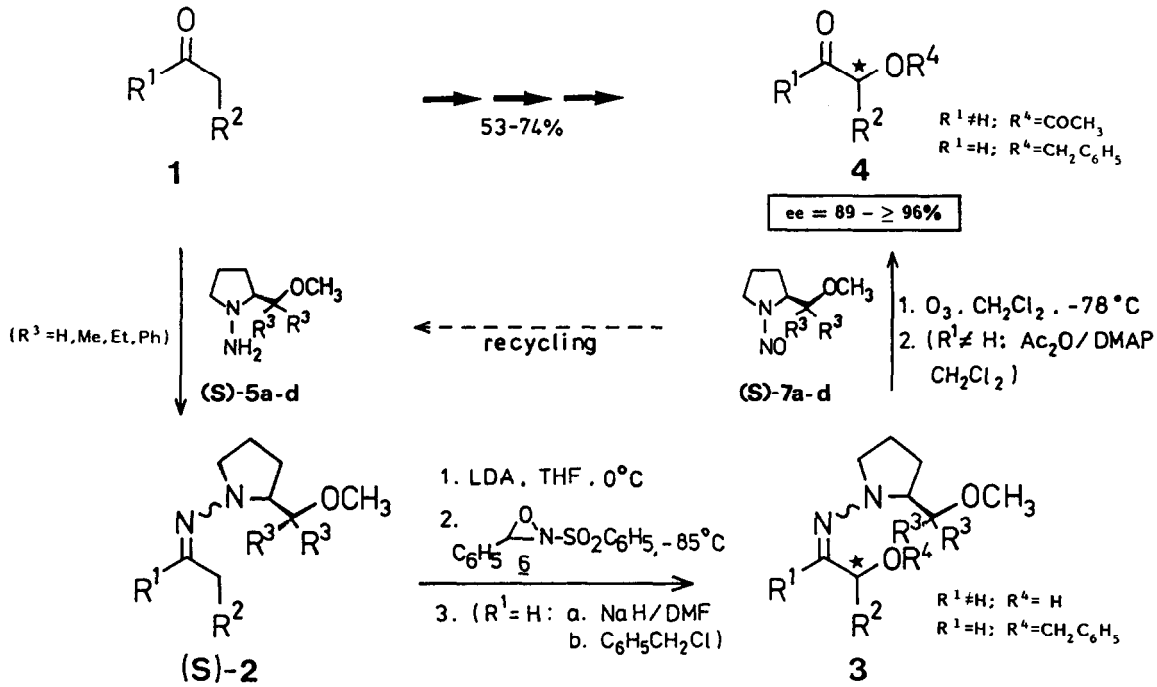
Summary: α-Benzyloxy aldehydes and α-acetoxy ketones **4** of high enantiomeric purity are prepared in good overall yields via oxaziridine mediated hydroxylation of chiral hydrazone azaenolates. As auxiliaries novel proline derived hydrazine reagents **5** are used.

The importance of α-hydroxy carbonyl compounds as crucial structural features of many natural products and as chiral building blocks initiated numerous studies for their stereoselective synthesis[1]. An attractive route to this versatile class of compounds is the direct oxidation of the parent carbonyl compounds and their enolates[2] or enol derivatives[3]. Consequently, overall enantioselective procedures using this approach have been developed recently[4]. With one exeption[4f], all of these new techniques lead to α-hydroxy acid derivatives. Thus, the efficient α-hydroxylation of simple aldehydes and ketones affording protected α-hydroxy synthons of type **A** and **B** remains to be solved.





In continuation of our efforts to further explore the utility of the SAMP-/RAMP-hydrazone methodology[5], we describe herein the enantioselective synthesis of α-benzyloxy aldehydes **A** and α-acetoxy ketones **B** in good overall chemical yields and of high enantiomeric purity. As is shown in the scheme, the aldehydes and ketones **1** are transformed into their corresponding SAMP-hydrazones ($R^3 = H$) or the sterically hindered hydrazones **(S)-2**, using novel hydrazine reagents **(S)-5b-d** ($R^3 = Me, Et, Ph$)[6] with sterically more demanding side chains at the pyrrolidine ring. After deprotonation with tert-butyllithium or lithium diisopropylamide (1.1 equ.) in tetrahydrofuran ($0°C$,



5h), the resulting chiral azaenolates underwent facile oxidation by treatment with 2-(phenylsulfonyl)-3-phenyloxaziridine (**6**)[2c] (1.5 equ., $-85°C \rightarrow -50°C$, 1.5h). After quenching with saturated ammonium chloride solution and workup with ether, the α–hydroxy hydrazones **3** ($R^4 = H$) are isolated after flash chromatography (silica gel, ether–n-pentane, 30:70).

The diastereomeric excess of **3** ($R^4 = H$) is easily determined either by ^{13}C NMR spectroscopy or by HPLC (see footnote h, table). Whereas in the case of ketones ($R^1 \neq H$) no other diastereomer was detectable (de $\geq$ 96%), the aldehyde hydrazones ($R^1 = H$) showed lower de's (footnote h–k, table) and separation of the minor diastereomer was neccessary by flash chromatography at this stage. The α–hydroxy hydrazones of ketones are cleaved by ozonolysis in dichloromethane at $-78°C$ to yield the highly enantiomerically enriched α–hydroxy ketones **4** ($R^4 = H$). The enantiomeric excess was determined by ^1H NMR shift experiments using $Eu(hfc)_3$ on the corresponding acetates ($R^4 = COCH_3$) prepared with Ac_2O, DMAP in dichloromethane. The diastereomerically pure α–hydroxy hydrazones of aldehydes are first benzylated with sodium hydride and benzyl chloride in dry dimethylformamide, followed by oxidative cleavage with ozone to yield the enantiomerically pure α–benzyloxy aldehydes **4** ($R^4 = CH_2C_6H_5$). Recycling of the chiral auxiliary **(S)-5a-d** is possible via separation of the corresponding nitrosamines **(S)-7a-d** formed during ozonolysis[5].

The results summarized in the table show that LDA is superiour over t–BuLi as base giving better overall chemical yields (entry 2–7). In the case of ketone hydroxylations SAMP **(5a)** and **5d** ($R^3 = Ph$, entry 7) are the auxiliaries of choice, whereas the asymmetric inductions of aldehyde hydroxylations are best using **5c** ($R^3 = Et$) as hydrazine reagent (entry 10–12). The other enantiomers of 4 may be obtained in the same way by employing the corresponding auxiliaries based on (R)–proline (entry 4,5).

The absolute configurations of the final products are in agreement with a metallo retentive mechanism, which we postulated previously for electrophilic substitutions via SAMP–/RAMP–hydrazones[5]. However, unpredicted absolute configurations are noticed in the aldehyde hydroxylations by chanching SAMP to the more hindered auxiliaries (entry 8–12).

In conclusion, the asymmetric oxaziridine mediated α–hydroxylations described here offer a new overall enantioselective route to protected α–hydroxy aldehydes and ketones[9].

Table 1. Highly enantiomerically enriched α–benzyloxy aldehydes and α–acetoxy ketones **4** prepared by asymmetric hydroxylation of metalated chiral hydrazones **2**.

Entry	R^1	R^2	R^3	R^4	base	overall yield[%][a]	$[\alpha]_D^{20}$(c,benzene)	ee[%][b]	confg.
1	C_6H_5	CH_3	H	$COCH_3$	LDA	51 (60)	+33.2° (1.16)	93	(R)[c]
2	C_6H_5	CH_3	CH_3	$COCH_3$	t-BuLi	51 (62)	+27.5° (1.0)	85	(R)
3	C_6H_5	CH_3	CH_3	$COCH_3$	LDA	73 (86)	+31.4° (1.05)	88	(R)
4	C_6H_5	C_6H_5	H	$COCH_3$	t-BuLi	54 (62)	-230.5° (1.0)	≥96	(R)[d]
5	C_6H_5	C_6H_5	H	$COCH_3$	LDA	74 (82)	+231.3° (1.0)	≥96	(S)[e]
6	$C_6H_5CH_2$	C_6H_5	H	$COCH_3$	t-BuLi	48 (52)	+74.1° (1.0)	36	(R)
7	$C_6H_5CH_2$	C_6H_5	C_6H_5	$COCH_3$	LDA	62 (75)	+202.0° (1.0)	89[f]	(R)
8	H	$n-C_6H_{13}$	H	$CH_2C_6H_5$	LDA	63 (82)	+43.2° (0.95)	56	(R)
9	H	$n-C_6H_{13}$	CH_3	$CH_2C_6H_5$	LDA	44[g] (85)	-74.7° (1.0)	≥96[h]	(S)
10	H	$n-C_6H_{13}$	C_2H_5	$CH_2C_6H_5$	LDA	55[g] (80)	-75.0° (1.0)	≥96[i]	(S)
11	H	$C_6H_5CH_2$	C_2H_5	$CH_2C_6H_5$	LDA	66[g] (83)	-110.9° (0.9)	≥96[j]	(S)
12	H	$n-C_4H_9$	C_2H_5	$CH_2C_6H_5$	LDA	53[g] (70)	-78.3° (1.05)	≥96[k]	(S)[8]

a) Overall yield of the process **1** → **4**; in parentheses: yield of oxidation step **2** → **3**. – b) Determined with the ^{1}H NMR shift reagent Eu(hfc)$_3$. – c) (S)-2-Hydroxy-1-phenylpropanone[4f]: $[\alpha]_D$=–86.7° (c=2.0, $CHCl_3$); this work: $[\alpha]_D^{20}$=+83.7° (c=2.1, $CHCl_3$). – d) (S)-(+)-Benzoin[7]: $[\alpha]_D^{25}$ =+118.4° (c=2.5, acetone); this work: $[\alpha]_D^{22}$ =+116.3° (c=1.2, acetone). – e) RAMP was used as chiral auxiliary. – f) Partial epimerization/racemization; de of corresponding hydrazone **3** 98% (^{13}C NMR). – g) After separation of the minor diastereomer of hydrazone **3** by flash chromatography (silica gel, ether-n-pentane, 30:70). – h) Diastereomeric ratio of **3** 66:34 determined by HPLC: Resolve column (Waters, 5 μ spherical silica, 3.9x150 mm) coupled with a Pirkle column [Serva, Heidelberg, (R)-N-dinitrobenzoylphenylglycine covalently bound on SI 100 polyol, 4.6x250 mm], n-hexane-isopropanol, 95:5; 0.5 ml/min, 520 psi. – i) Diastereomeric ratio = 90:10 (HPLC). – j) Diastereomeric ratio = 97:3 (HPLC). – k) Diastereomeric ratio = 88:12 (HPLC).

Acknowledgements: V.B. thanks the Alexander von Humboldt-Stiftung for a fellowship. The financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank the chemical industry (Degussa AG, BASF AG, Bayer AG and Hoechst AG) for generously providing us with chemicals.

REFERENCES AND NOTES

1. For general approaches not involving α-hydroxylation see: a) T. Mukaiyama, Y. Sakito, M. Asami, *Chem. Lett.* **1979**, 705; M. Asami, T. Mukaiyama, *ibid.* **1983**, 93. – b) A. I. Meyers, J. Slade, *J. Org. Chem.* **45** (1980) 2785. – c) D. Seebach, R. Naef, *Helv. Chim. Acta* **64** (1981) 2704. – d) G. Fráter, U. Müller, W. Günther, *Tetrahedron Lett.* **22** (1981) 4221. – e) M. M. Midland, P. E. Lee, *J. Org. Chem.* **46** (1981) 3933. – f) J. K. Whitesell, A. Bhattacharya, K. Henke, D. Aguilar, *J. Chem. Soc., Chem. Commun.* **1982**, 988, 989. – g) G. Guanti, E. Narisano, L. Banfi, C. Scolastico, *Tetrahedron Lett.* **24** (1983) 817. – h) D. Enders, H. Lotter, N. Maigrot, J.–P. Mazaleyrat, Z. Welvart, *Nouv. J. Chim.* **8** (1984) 747. – i) H. C. Brown, G. G. Pai, P. K. Jadhav, *J. Am. Chem. Soc.* **106** (1984) 1531. – j) J. E. Lynch, E. L. Eliel, *J. Am. Chem. Soc.* **106** (1984) 2943. – k) G. Helmchen, R. Wierzchowski, *Angew. Chem.* **96** (1984) 59; *Angew. Chem. Int. Ed. Engl.* **23** (1984) 60.

2. For some leading references see: a) E. Vedejs, D. A. Engler, J. E. Telschow, *J. Org. Chem.* **43** (1978) 188; E. Vedejs, S. Larsen, *Org. Synth.* **64** (1985) 127. – b) T. Cuvigny, G. Valette, M. Larcheveque, H. Normant, *J. Organomet. Chem.* **155** (1978) 147. – c) F. A. Davis, L. C. Vishwakarma, J. M. Billmers, J. Finn, *J. Org. Chem.* **49** (1984) 3241. – d) R. M. Moriarty, K.–C. Hou, *Tetrahedron Lett.* **25** (1984) 691. – e) N. K. Dunlap, M. R. Sabol, D. S. Watt, *Tetrahedron Lett.* **25** (1984) 5839.

3. For some recent examples see: a) J. P. McCormick, W. Tomasik, M. W. Johnson, *Tetrahedron Lett.* **22** (1981) 607. – b) T. V. Lee, J. Toczek, *ibid.* **23** (1982) 2917. – c) G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve, Jr., C. W. Kim, *J. Org. Chem.* **48** (1983) 4940; G. M. Rubottom, J. M. Gruber, H. D. Juve, Jr., D. A. Charleson, *Org. Synth.* **64** (1985) 118. – d) C. Iwata, Y. Takemoto, A. Nakamura, T. Imanishi, *Tetrahedron Lett.* **26** (1985) 3227. – e) R. V. Hoffmann, C. S. Carr, B. C. Jankowski, *J. Org. Chem.* **50** (1985) 5148. – f) R. M. Moriarty, O. Prakash, M. P. Duncan, R. K. Vaid, *ibid.* **52** (1987) 150. – g) F. A. Davis, A. C. Sheppard, *ibid* **52** (1987) 955.

4. a) R. Gamboni, P. Mohr, N. Waespe–Šarčevič, C. Tamm, *Tetrahedron Lett.* **26** (1985) 203; R. Gamboni, C. Tamm, *Helv. Chim. Acta* **69** (1986) 615. – b) W. Oppolzer, P. Dudfield, *ibid.* **68** (1985) 216. – c) D. A. Evans, M. M. Morrissey, R. L. Dorow, *J. Am. Chem. Soc.* **107** (1985) 4346. – d) F. A. Davis, L. C. Vishwakarma, *Tetrahedron Lett.* **26** (1985) 3539. – e) F. A. Davis, M. S. Haque, T. G. Ulatowski, J. C. Towson, *J. Org. Chem.* **51** (1986) 2402. – f) F. A. Davis, M. S. Haque, *ibid.* **51** (1986) 4085. – g) M. P. Gore, J. C. Vederas, *ibid.* **51** (1986) 3700 . – h) F. A. Davis, T. G. Ulatowski, M. S. Haque, *ibid.* **52** (1987) 5288.

5. Review: D. Enders in *Asymmetric Synthesis (J. D. Morrison, Ed.) vol.* **3**, p. 275, Academic Press, Orlando 1984; D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **65** (1987) 173, 183; Most recent application: D. Enders, B. Bhushan Lohray, *Angew. Chem.* 99 (1987) 359; *Angew. Chem. Int. Ed. Engl.* 26 (1987) 351.

6. D. Enders, H. Kipphardt, L. J. Breña Valle, V. Bhushan: unpublished results; H. Kipphardt, dissertation, Technical University Aachen 1986; L. J. Breña Valle, dissertation, UNAM, Mexico City, in preparation.

7. J. Kenyon, R. L. Patel, *J. Chem. Soc.* **1965**, 435.

8. H. Hagiwara, K. Kimura, H. Uda, *J. Chem. Soc., Chem. Commun.* **1986**, 860.

9. The spectroscopic data (IR, NMR, MS) and elementary analyses of all new compounds are in agreement with the structures given.

(Received in Germany 7 March 1988)